UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: July 27, 2016

SUBJECT: **Penflufen:** Summary of the Hazard and Science Policy Council (HASPOC) Meeting of April 28th, 2015: Recommendations on Waiver Requests for Subchronic Inhalation Toxicity and Comparative Thyroid Studies.

PC Code: 100249
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0053477
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS No.: N/A
40 CFR: N/A

FROM: Uma Habiba
Executive Secretary, HASPOC
Health Effects Division (7509P)

THROUGH: Jeffrey Dawson, Co-Chair
LCDR Jonathan Leshin, Ph.D., Co-Chair
HASPOC
Health Effects Division (HED; 7509P)
Antimicrobial Division (AD7510P)

TO: Karlyn Middleton, Toxicologist
Christina Swartz, Chief
Registration Action Branch 2
Health Effects Division (7509P)

MEETING ATTENDEES:

HASPOC Members: Anna Lowit, Elissa Reaves, Elizabeth Mendez, Jeff Dawson, John Kough, Kristin Rury, Jonathan Leshin, Julie Van Alstine, Michael Metzger, Ray Kent, P.V. Shah

Presenters: Karlyn Middleton, Gerad Thornton, Janet Cowins

Other Attendees: Connor Williams, Jessica Kidwell, Myron Ottley, Sarah Dobreniecki

I. PURPOSE OF MEETING:

Risk Assessment Branch 2 (RAB2) is currently preparing a human health risk assessment to support seed treatment uses for the fungicide penflufen. The toxicology database for penflufen is complete with the exception of a subchronic inhalation toxicity study and a comparative thyroid study. The Hazard and Science Policy Council (HASPOC) met on April 28, 2016 to discuss the need for the outstanding toxicity studies to support the uses of penflufen.

II. SUMMARY OF USE PROFILE, TOXICITY PROFILE & PREVIOUS RISK ASSESSMENT:

Penflufen is a pyrazole carboxamide fungicide primarily used as a seed treatment for a number of agricultural crops. Exposure to penflufen is via the diet (food and drinking water) from residues present in foods grown from penflufen treated seeds. There are no residential uses of penflufen, so exposure in residential and non-occupational settings is not anticipated. Occupational exposures are expected for handlers working in commercial seed treatment operations (e.g., primary handlers such as loader/applicator, sewer, bagger and multiple activities workers, as well as secondary handlers such as planters). Post-application exposure is not likely since sustained levels of contact with treated seed after it has been planted would not be expected. All end-use products are formulated as a flowable concentrate (FS).

The liver and thyroid are target organs for penflufen. Liver and/or thyroid effects were seen in rats, mice and dogs after subchronic and/or chronic exposure. No evidence of quantitative/qualitative susceptibility was seen in developmental toxicity studies (rats and rabbits). Qualitative sensitivity of the young (delayed sexual maturation and decreased litter size) was seen in the 2-generation reproduction study. However, these effects are well characterized, and there is a clear NOAEL for the effects seen. Decreased motor/locomotor activity was observed in rats following acute (both sexes) and subchronic (females only) oral exposure in neurotoxicity studies; neuropathological lesions were not observed in either study. Penflufen is classified as having "suggestive evidence of carcinogenicity, based on limited evidence for carcinogenicity (histiocytic sarcomas in male rats). There is no concern for mutagenicity. Penflufen has low toxicity in acute lethality studies via the oral, dermal (Toxicity Category III), and inhalation routes of exposure (Toxicity Category IV). It is not an eye or dermal irritant (Toxicity Category IV) or dermal sensitizer.

Penflufen is well-absorbed in rats following oral dosing. Overall recovery of the total administered radioactivity in the urine, feces, organs, tissues, gastro-intestinal tract (GIT) and/or bile was between 94-97% in both male and female rats. Absorption of radiolabeled penflufen began immediately after oral (gavage) administration and maximum plasma concentrations were reached between 40 minutes and 1.5 hours after dosing. The percent absorption of radiolabeled penflufen based on recoveries of radioactivity in the bile, urine and body, excluding GIT, was ≈ 91% of the administered dose. Penflufen was extensively metabolized in the rat. Metabolic reactions were detected in ten different positions of the molecule and a large number of metabolites were formed. There were no different metabolites found in males and females, but the amount of some metabolites was different with regard to sex. The main metabolic reactions were demethylation in the pyrazole ring or hydroxylation reactions occurring in the alkyl side chain of the phenyl ring, in the position 4' of the phenyl ring and in the methyl group at position 3 of the pyrazole ring. Of the

hydroxylation reactions determined, most were detected as trihydroxy and dihydroxy compounds, with only a minor portion of the metabolites hydroxylated in only a single position.

In the most recent assessment (D387450, D. Davis), the endpoints and points of departure (PODs) were selected for acute and chronic dietary, and occupational and residential (chosen despite no residential exposures anticipated) inhalation exposure. For acute dietary exposure, the rat acute neurotoxicity study was used with a NOAEL of 50 mg/kg/day, based on decreased motor and locomotor activity at the LOAEL of 100 mg/kg/day. For chronic dietary exposure, the chronic dog was used with a NOAEL of 38 mg/kg/day, based on body weight changes, clinical chemistry, liver, thyroid, and adrenal effects at the LOAEL of 357 mg/kg/day. A dermal risk assessment was not conducted since a dermal hazard was not identified in a dermal toxicity study and there is no concern for increased quantitative susceptibility. For short-term inhalation exposure, the subchronic dog study with a NOAEL of 55.7 mg/kg/day, based on body weight changes, clinical chemistry, liver, and adrenal effects seen at the LOAEL of 532 mg/kg/day was selected. The chronic dog was used for intermediate-term exposure, with a NOAEL of 38 mg/kg/day, based on body weight changes, clinical chemistry, liver, thyroid, and adrenal effects at the LOAEL of 357 mg/kg/day. The 10X FQPA safety factor for the protection of infants and children, was reduced to 1X based on the following: The risk assessments are based on the most sensitive endpoints in the toxicity database; the NOAELs selected for risk assessment are considered protective of all potential toxicity; and highly conservative exposure estimates were incorporated into the risk assessment.

III. STUDY WAIVER REQUESTS

a. Inhalation Toxicity Study

Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether or not an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including its: (1) degree of irritation and corrosivity; 2) volatility; 3) aerosol particle size; and 4) Acute Toxicity Category and extrapolated margins of exposure (MOEs) (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral points of departure (PODs) were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some cases the inhalation PODs were significantly more sensitive. Currently, OPP uses a weight of the evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 Science Advisory Panel (SAP). As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

1. **Physical Chemical Properties:** Vapor pressure and Henry's law constant are key considerations with respect to volatilization after sprays have settled. However, low vapor

pressure and/or Henry's law constant do not preclude exposure to aerosolized droplets or particles/dust. Penflufen has a low vapor pressure of 9.0×10^{-9} mm Hg at 25ºC. The Henry's law constant is 1.04×10^{-10} atm·m^3/mol.

2. **Use pattern & exposure scenarios:** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. Penflufen is formulated as a flowable concentrate (FS). Occupational inhalation exposures are expected for handlers working in seed treatment operations (e.g., primary handlers which include loader/applicator, sewer, bagger, and multiple activities workers, as well as for secondary handlers which includes planters). Based on the use pattern, the duration of exposure is expected to be short- and intermediate-term. Long-term exposures (i.e., more than 6 months of continuous exposure) are not expected to occur. Respirators are not required on the registered labels for any of the registered uses of penflufen during handler activities. Post-application occupational inhalation exposures are expected to be negligible for the registered uses of penflufen. There are no residential uses for penflufen.

3. **Margins of Exposure (MOEs):** MOE estimates for inhalation scenarios were calculated using an oral toxicity study and should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern (LOC) as a benchmark for granting waiver requests. The 2009 analysis suggests this approach is appropriate for most pesticides, but not all. Using this interim WOE approach, MOEs from 10-100 times greater than the LOC will be considered in combination with other factors discussed here. The LOC for occupational workers is 100 based on 10X for interspecies extrapolation and 10X for intraspecies extrapolation. All handler inhalation MOEs were calculated using the inhalation POD selected for intermediate-term inhalation (most conservative) exposure from a chemical specific oral chronic dog study (NOAEL= 38 mg/kg/day). All the inhalation MOEs ranged from 41,000 to 250,000,000 for workers using baseline level of protection (i.e., no respirator) and were not of concern (MOEs > 1,000).

4. **Evidence in the database of toxicology studies for other pesticides:** When considering a waiver request for an inhalation toxicity study, the Agency will attempt to evaluate other pesticides which share the same mode of action (MOA) and/or are in the same chemical class. These pesticides can provide important information with respect to potential inhalation toxicity. Specifically, if other similar pesticides show inhalation toxicity studies to be more sensitive, an inhalation toxicity study may be required regardless of MOE, depending on the exposure profile. The risk assessment team conducted a data search using the Integrated Structure, Toxicology, Endpoints and Properties (ISTEP) database for other pyrazole carboxamide pesticides. Other pyrazole carboxamides identified include: benzovindiflupyr, fenpyrazamine, sedaxane, fluxapyroxad, tolfenpyrad, isopyrazam, penthiopyrad, tebufenpyrad, halosulfuron methyl and chlorantriniliprole. Of the chemicals identified, tolfenpyrad was the only one with inhalation toxicity studies (range finding and main); together, the studies were used to establish a NOAEL of 2.6 mg/kg/day and a LOAEL of 6.8 mg/kg/day (based on body weight changes and mortality) for inhalation risk assessment. The systemic effects seen in the tolfenpyrad inhalation study were not more sensitive than those observed in oral studies. Also, no portal of entry effects were seen in the inhalation study. Six pyrazole carboxamides (benzovindiflupyr

fluxapyroxad, fenpyrazamine, oxathiapiprolin, penthiopyrad, and sedaxane) have been evaluated by the HASPOC and the inhalation study requirement has been waived for all of them.

5. **Inhalation Toxicity for Penflufen:** In the acute lethality inhalation study in rats at 2.0225 mg/L (365 mg/kg/day), the only dose tested), decreased rectal temperature (exposed: males: 35.0° C; females: 34.4° C; controls: males: 38.0° C; females: 38.0° C) and clinical signs (piloerection, bradypnea, labored breathing patterns, dyspnea, breathing sounds, reduced motility, limp, high-legged gait, staggering gait, and red encrustations on the nose) were observed. Most signs of toxicity were gone by day 1; all rats were clear of signs by day 4. There was no mortality observed in the study.

   Based on a WOE approach, considering all of the available hazard and exposure information, the HASPOC recommends that the subchronic inhalation toxicity study not be required for penflufen. This approach considered all of the available hazard and exposure information for penflufen including: 1) the physiochemical properties for penflufen; 2) the hazard profile of penflufen (available inhalation toxicity data and its target organs); and 3) using the current oral POD, the MOEs are not of concern as the lowest MOE was 41,000 for workers planting treated seeds of the Bulb vegetable crop group 3-07.

b. Comparative Thyroid Study

A number of pesticides have been shown to perturb thyroid hormone homeostasis via reduction of circulating thyroid hormones[1]. This perturbation may be the initial, critical effect leading to adverse effects on the developing nervous system[2,3]. When a chemical causes thyroid effects, there is inherent uncertainty about potential impacts to the developing brain in response to changing thyroid levels. There is also a lack of empirical data on whether pregnant women or the fetus are more or less susceptible, compared to adults, to the impact of chemicals that alter thyroid hormone homeostasis. This gap makes predictions on developmental susceptibility based on data from adult organisms difficult and very uncertain. The current 40 CFR Part 158 Toxicology Data Requirements do not include thyroid hormone measurements during these potentially sensitive lifestages. The EPA has developed guidance for conducting a comparative thyroid assay[4] that uses a mechanistic approach to generate thyroid-specific data which can address the uncertainties associated with lifestage susceptibility and allow for the establishment of PODs that would be protective of potential effects of thyroid function disruption in pregnant females on the fetus and newborn.

1. Thyroid Toxicity

[1] Hurley et al. 1998. Mode of carcinogenic action of pesticides inducing thyroid follicular cell tumors in rodents. Environ. Health Perspect. 106(8): 437-445.
[2] Chan S and Kilby MD. 2000 Thyroid hormone and central nervous system development. J Endocrinol 165:1-8
[3] Fisher DA. 2000. The importance of early management in optimizing IQ in infants with congenital hypothyroidism. J Pediat 136:274-274.
[4] US EPA 2005. Guidance for Thyroid Assays in Pregnant Animals, Fetuses and Postnatal Animals, and Adult Animals. Washington, DC.

In the available toxicity data from adult animals, there is evidence that the thyroid is a target organ for penflufen. After repeat exposure, changes in thyroid weight, as well as gross and histopathological thyroid changes were seen in rats in multiple studies at ≥ 288 mg/kg/day. Thyroid effects were also observed in dogs (≥357 mg/kg/day) and mice (880 mg/kg/day) after chronic exposure at doses similar to or higher than those in the rat. The thyroid effects (along with liver) are currently included in the LOAEL for the study selected for chronic dietary and inhalation (intermediate-term) risk assessments. Thyroid hormones were not measured in the available studies for penflufen. Therefore, there are no data regarding the potential effects of penflufen on thyroid homeostasis in adults or infants and children. Also, there is little understanding of the pharmacodynamic differences of penflufen exposure in adult vs. the young. This lack of characterization creates uncertainty with regards to potential life stage sensitivities due to exposure to penflufen, and raises the agency's level of concern.

2. Risk Implications

Based on the use pattern (seed treatment only),. exposure to penflufen is via the diet (food and water) from foods grown from penflufen treated seeds. Occupational exposures also occur to handlers working in commercial seed treatment operations and those involved with planting treated seeds. Post-application occupational exposure is not anticipated and there are no residential uses for penflufen. Using the current points of departure, the risk estimates for penflufen are low for all potential exposure scenarios. Based on highly conservative dietary risk assessments, the estimated exposure (food and water) to the U.S. population and all modeled populations from the proposed uses of penflufen resulted in an estimated risk equivalent to <5% of the acute population adjusted dose (aPAD) and <2% of the chronic population adjusted dose. For exposure assessments, all handler inhalation MOEs ranged from 41,000 to 250,000,000 for workers using baseline level of protection (i.e., no respirator). A dermal assessment was not conducted since a dermal hazard was not identified for penflufen.

Based on a WOE approach, the HASPOC concludes that a comparative thyroid assay (comparing pregnant animals, fetuses, postnatal animals, and adult animals) is not required for penflufen at this time. Although thyroid toxicity was observed in adult animals in the toxicological database for penflufen, the current PODs selected for risk assessment are adequately protective of potential thyroid effects in the young. Using the current PODs, risk estimates are extremely low for the current uses and provide an adequate margin of safety to protect for any potential lifestage susceptibilities. **However, the need for the comparative thyroid study will be revisited if the use pattern changes or if updated risk estimates reach a point where potential lifestage susceptibility is no longer adequately covered.**

IV. HASPOC RECOMMENDATIONS

The HASPOC, based on a WOE approach considering of all the available hazard information, concludes that subchronic inhalation toxicity study and the comparative thyroid study **are not required** at this time.

In determining the need for a subchronic inhalation study, EPA's WOE decision process included both hazard and exposure considerations as well as incorporation of a presumed 10X database uncertainty factor (UF_{DB}) for the lack of this study. Thus, the Agency's level of concern in the

HASPOC's WOE evaluation for inhalation exposure risk assessment is a target MOE of 1,000 which includes the 10X inter-species extrapolation, 10X intra-species variation, and the 10X UFDB. In case of penflufen, all handler occupational and residential inhalation MOEs were higher than the LOC of 1000 when using an oral POD This indicates that the lack of an inhalation study does not reduce the overall confidence in the risk assessment or result in an uncertainty (i.e., that study will not provide a POD sufficiently low to result in a risk of concern).